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Tiagabine-related non-convulsive status epilepticus in partial epilepsy: three case reports and a review of the literature

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There have been several recent reports of non-convulsive status epilepticus during tiagabine therapy in patients with partial epilepsy. We report three cases where elevation of tiagabine dosage was followed by electroclinical features, or electroencephalographic features without clinical signs, of non-convulsive status epilepticus. Administration of clonazepam and/or discontinuation to tiagabine lead to complete remission. In one case after re-exhibition of tiagabine the EEG again showed rhythmic delta waves. We review the other cases reported so far and discuss the different pathophysiological hypotheses about the association in the light of new experimental data.

Key words: tiagabine; partial epilepsy; non-convulsive status epilepticus; GABA receptor; review.

INTRODUCTION

Tiagabine (TGB), a nipecotic acid analogue, is a relatively new anticonvulsant agent. It is a potent and selective inhibitor of the reuptake of GABA from the synaptic cleft into neurons and glial cells and therefore increases the synaptic concentration of GABA[1,2]. It is metabolized in the liver, predominantly by a cytochrome P450 enzyme[1]. TGB has been approved for the adjunctive treatment of partial seizures in the European Union, the USA, Australia and New Zealand[3].

It seems to be a relatively safe drug, adverse events being mostly mild or moderate, related to the typical side effects of anticonvulsants (dizziness, headache, somnolence, ataxia)[1,3,31]. Like some other anticonvulsants with a good effect on partial seizures, it was found to increase the frequency and duration of generalized spike-wave discharges in animal models.

However, there have been several recent reports of tiagabine-associated non-convulsive status epilepticus (NCSE) in patients not only with generalized epilepsies[4,5], but also with partial epilepsies[4,6–11,33]. Paradoxical effects of anticonvulsants are not unknown, but seem to be sporadic and often associated with intoxication[12,13]. In the case of tiagabine, the events occurred within the range of therapeutic doses and serum concentrations. In this report we describe another three patients with partial epilepsy and NCSE during treatment with tiagabine, compare the cases with the other cases reported so far, and discuss the different hypotheses about possible underlying pathomechanisms.

Case 1

In 1991 a 29-year-old patient suffered for the first time from complex partial seizures (CPS), starting with a feeling of dyspnoea and leading to reduction of alertness, often followed by loss of consciousness and amnesia. Manual automatisms and blank staring were usually noticed. The seizures typically lasted some minutes and appeared in clusters of four to six seizures every 4–6 weeks.

Cranial MRI showed the residue of a small bleed from a cavernoma in the left thalamus but no cortical lesion. Neurologic examination was completely normal. The EEG repeatedly showed slow activity with

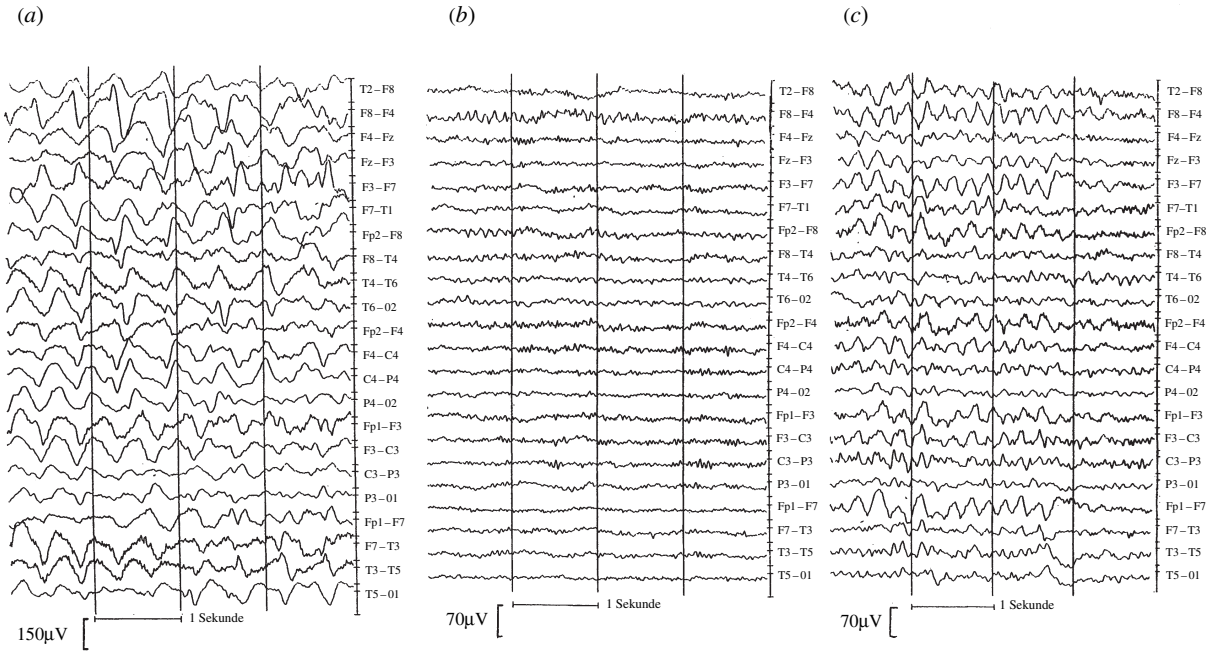

Fig. 1: EEG-findings of our patient. (*a*) EEG performed while patient received 30 mg tiagabine and showed clinical signs of non-convulsive status epilepticus, (*b*) EEG after administration of clonazepam and discontinuation of tiagabine, (*c*) EEG after re-exhibition to 30 mg tiagabine under protection of clonazepam.

rare sharp waves in the left as well as the right frontotemporal regions, but never generalized epileptic activity. Anticonvulsive therapy with phenytoin (max. 300 mg/day) did not reduce the frequency of seizures significantly in spite of high serum concentrations ($>30\ \mu g\ ml^{-1}$) and clinical signs of intoxication.

Because of the patient's liver cirrhosis following hepatitis C infection after blood transfusion during the treatment of a monocytic leukaemia in 1980, phenytoin was replaced by gabapentin in 1996. This reduced seizure frequency to one or two seizures per month, but did not control the seizures even with high doses on the borders of tolerability. In 1997 therapy was changed to carbamazepine monotherapy, but seizure control could not be established either, even at high dosage and serum concentration (1350 mg/day–13.1 $\mu g\ ml^{-1}$) and signs of intoxication (ataxia, dizziness).

Therefore, adjunctive therapy with tiagabine was started in 1998. Within 3 months the dosage was increased step by step while carbamazepine was reduced to avoid central nervous side effects. With a combination of tiagabine (25 mg/day, serum concentration 41 ng ml^{-1}) and carbamazepine (600 mg/day, serum concentration 6.7 $\mu g\ ml^{-1}$), the seizure frequency was further reduced, but in the summer of 1999, the patient still had one seizure every 3 months.

Therefore the tiagabine dose was increased to 30 mg/day (10 mg tid) in December 1999. Four days after the increase the treating physician noticed stereotypic oral and manual movements and a reduced responsiveness from the patient. In a neurologic examination no focal deficits were found. One hour after the symptoms had started, the EEG showed high voltage, generalized, rhythmic delta activity (2–3/second) with several sharp waves (Fig. 1(a)). Assuming tiagabine-induced NCSE, the tiagabine administration was stopped and clonazepam (3 mg i.v.) was given. The patient recovered completely, and the EEG showed pharmacologically induced precentral beta activity and intermittent alpha-activity above the right frontotemporal region (Fig. 1(b)).

To support the suspicion of tiagabine-induced NCSE, after obtaining informed consent from the patient re-exhibition with 3×10 mg tiagabine was started 3 days later (serum-concentration 120 ng ml^{-1}) under the protection of a continuous i.v.-administration of clonazepam (4 mg/day). The patient remained alert and conscious; no seizures were seen. However, the EEG again showed intermittent rhythmic bilateral frontal theta-activity (Fig. 1(c)). Therefore, tiagabine was discontinued. Three days later, this EEG activity had significantly reduced.

Finally carbamazepine, which had been administered unchanged throughout these events, was replaced by oxcarbazepine (900 mg/day). The patient remained seizure free during a 5 month follow-up period.

Case 2

Since 1993 this 30-year-old female patient has suffered from simple partial sensomotor seizures of the left arm and leg. Apart from two tonic–clonic seizures in 1993 no seizures with impairment of consciousness had been reported. An EEG showed no epileptic activity, but rare intermittent focal slowing in both left and right temporal regions. A MRI showed non-specific paraventricular parietal white matter lesions but no cortical lesions were found.

Primidone and gabapentin, even in high doses, did not control the seizures. Carbamazepine and lamotrigine caused allergic skin rashes and had to be discontinued. In 1998 therapy was changed to valproate which initially reduced seizure frequency. A few months later seizure frequency rose again despite elevation of the valproate dose. A maximum dose of 1800 mg/day (96 ug ml^{-1}) lead to intoxication. A daily dose of 1650 mg valproate was tolerated well, but seizure frequency remained unchanged (max. two seizures/day).

In February 2000 topiramate was added (max. 350 mg/day, 12.73 ug ml^{-1}), but frequency as well as duration of the seizures further increased. In June 2000 topiramate was step by step replaced by tiagabine while valproate was left unchanged. Misunderstanding the prescription, the patient increased her tiagabine dose to 25 mg/day within 2 weeks.

One week later, having been coincidentally admitted to a neurological ward to diagnose the aetiology of the white matter lesions, suddenly the patient was found disoriented and confused. An EEG showed generalized blunt delta waves of high amplitude and sharp slow waves. After administration of 1 mg clonazepam i.v. the rhythmic EEG patterns subsided. The patient was tired but fully oriented. Tiagabine was tapered completely within 2 weeks. Valproate was elevated to 2000 mg/day without signs of intoxication. The EEG showed a slight general slowing, but no rhythmic patterns and no epileptiform discharges. During a 5-month follow-up no similar episode occurred.

Case 3

For 11 years the patient suffered from complex-partial seizures with blurred vision and dyspnoea, followed by loss of consciousness and movements of arms and legs. The episodes were interpreted as cardiovascular syncope until, in 1999, an EEG after sleep deprivation showed a sharp-wave focus in the right temporal region. Cranial MRI was completely normal.

Anticonvulsive therapy with lamotrigine was initiated in September 1999, but had to be stopped due to an idiosyncratic skin reaction (rash). With gabapentin (max. 1200 mg/day) the patient became seizure-free, but developed dose-dependent headache so that gabapentin was tapered. In the following months a few seizures occurred again. Because the patient did not want to take an anticonvulsant which could influence contraception tiagabine was added in steps of 5 mg/week while tapering gabapentin completely.

The last seizure of the usual semiology was experienced with tiagabine 15 mg/day, but the patient reported short episodes where she had the feeling of a slight alteration of consciousness and ‘slow thinking’. These episodes occurred about four to five times during May and June 2000 (tiagabine 20 and 25 mg/day) and lasted from seconds up to 1 minute. At the end of June during a routine examination (6 weeks after reaching the maximum dose of 25 mg/day) an EEG was conducted and showed frequent episodes of generalized delta waves (2–3/second) and sharp waves, lasting 10–15 seconds. During the whole examination no alteration of consciousness, concentration nor psychomotor slowing was observed, neurologic examination was completely normal, and the patient did not report any unusual sensations.

Under coadministration of clobazam (15 mg/day) tiagabine was reduced to 15 mg/day. Two weeks later the patient remained seizure free and did not report any episodes of alteration of consciousness. An EEG showed some generalized theta and delta waves, and again sharp waves over the right temporal region were observed but no generalized rhythmic waves.

Tiagabine was tapered completely and substituted by valproic acid. Four months later no seizures and no episodes of alteration of consciousness had been reported. An EEG remained unchanged without any rhythmic waves.

DISCUSSION

Two of the patients suffered from an episode of reduced responsiveness and manual/oral automatisms after an increase of tiagabine dosage which could be diagnosed by an ictal EEG as NCSE. The diagnosis was confirmed by the immediate response to clonazepam. Regarding the impaired liver function of the patient, a sudden metabolic worsening is also a potential reason for the NCSE in case 1[14]. Routine laboratory tests showed no significant decrease of liver function, and the blood ammonia level was only slightly elevated, not increased compared to previous levels. The temporal correlation between the increase in tiagabine dose and the occurrence of symptoms, the positive re-exhibition (case 1) and the singularity of the episode seem to corroborate the crucial role of tiagabine in both cases.

During the last 5 years, there have been reports of 16 cases of tiagabine associated NCSE in patients with partial seizures (including these three cases). Table 1 shows important points of the reports.

All patients whose case reports contained sufficient data suffered from partial epilepsy for at least 8 years. Neither age nor sex seem to have influence on the occurrence of NCSE. Aetiology of the epilepsy is equally distributed among the patients. No patient had generalized epileptic activity in his routine EEG. In all cases but one, tiagabine was administered within the therapeutic range of 25–50 mg daily.

In patients with hepatic dysfunction the elimination of tiagabine is slowed and tiagabine serum concentration increased[15]. In case 1, impaired liver-function has probably altered the pharmacokinetics. But serum concentrations before, during and shortly after the event were within or near the lower limit of the therapeutic range. Comedication consisted of agents with a wide range of mechanisms of action. The association of CPS and NCSE with a sudden rise of carbamazepine-epoxide, as So and colleagues[16] described, probably does not play an important role for the majority of the reported cases. Comedication was administered in a relatively high, but stable dosage with the exception of a slight parallel increase (7, case 2) or decrease (10, case 1; our case 2) in three cases. An effect of comedication changes on tiagabine concentration or vice versa seems improbable because of the lack of a pharmacokinetic drug interaction with tiagabine which is proven for carbamazepine, phenytoin[17] and valproate[18].

In one of our patients (case 1) a confounding factor can be found. All but one author could confirm the clinical diagnosis of an NCSE (unresponsiveness, automatisms, staring) with generalized epileptic activity in the EEG. EEG-activity was described relatively uniformly as rhythmic, generalized slow activity, typically 2–3/second, with additional sharp waves.

Intravenous administration of benzodiazepines, or, in at least four cases, stopping tiagabine, terminated the symptoms and, if an EEG was repeated, the rhythmic activity as well. In two cases, tiagabine was re-administered and worsened the EEG.

In a retrospective analysis of patients to whom TGB was administered in clinical practice, we found an incidence of 3/56 for NCSE. In contrast to that, Shinnar *et al.*[19] analysed 113 cases of NCSE which occurred during tiagabine-therapy in 2468 patients. They found no increased risk for NCSE compared to that of other patients with intractable partial seizures. However, NCSE may have gone undetected. There were 13 patients where mental status change associated with generalized spike-wave patterns was reported during clinical trials and interpreted as tiagabine-intolerance. They might have been experiencing NCSE[6]. In a recent publication Shinnar *et al.*[34] compared study safety data concerning NCSE with data from cohorts of epidemiologic studies. They found no increased incidence of status epilepticus nor of NCSE in tiagabine-treated patients. Again, they interpreted several NCSE-like episodes as 'tiagabine-intolerance' without demonstrating operational criteria for their decision.

In one of our patients (case 3), no EEG was done during the spells, but an interictal EEG showed the same reversible alterations as in the other patients. To our knowledge no similar event during administration of tiagabine has been reported so far. This could be due to the non-specific and unspectacular nature of these episodes with very short alterations in consciousness which could have been missed in routine examinations. In a retrospective analysis of 56 patients in our clinic to whom tiagabine was administered as a clinical routine, at least three other patients with similar episodes were found, but only in two cases were these episodes considered as adverse events of tiagabine[30]. Probably such patient reports have been misinterpreted. Moreover, some patients may have failed to report similar episodes. Therefore the incidence of similar events may be underestimated.

There are different opinions about the underlying pathological mechanisms. Trinka *et al.*[9] suggested that tiagabine at high doses might inhibit all neuronal GABA-uptake and therefore lead to a depletion of GABA in the presynaptic neuron, which is supposed to underlie the generation of pharmacoresistant late recurrent discharges *in vitro*[20]. Therefore, the anticonvulsant effects of tiagabine would attenuate with higher doses. Indeed, in animal experiments, such an attenuating effect could be found[21]. The reason for this effect remains unclear. The affinity of tiagabine for neuronal reuptake transporters is markedly less than its affinity for glial transporters[22], and the inhibition of glial GABA-transport plays a crucial role in sustaining a high synaptic and presynaptic GABA level[23]. Thus, synaptic tiagabine concentration must be comparatively high to cause GABA-depletion.

Newer experimental data points to a slightly different mechanism, although they do not disprove the role of GABA-shortage in the presynaptic neuron as a consequence of long-lasting blockage of reuptake. In different animal models, tiagabine (and vigabatrin as well) has proabsence effects. In the lethargic (lh/lh) mouse model of absence seizures, tiagabine (and vigabatrin) increased seizure frequency, as well as duration, markedly[24]. In WAG/Rij-rats as a model of non-convulsive absence epilepsy, tiagabine increased both the number and mean duration of spike-wave discharges. This effect was seen especially at high dosage[25]. In an animal model of convulsive status epilepticus, the administration of tiagabine

Table 1: Reported cases of non-convulsive status epilepticus of patients with partial epilepsy.

Author	Age; sex	Epilepsy for . . . years	Aetiology	Daily dose of TGB at NCSE	TGB administered since	Comedication	EEG during NCSE	NCSE terminated by	Procedure after NCSE
Balslev et al. 2000 (1)	12; f	not known	sympt	22.5 mg	not known	VGB	not done	Dosage reduction TGB	Reduction of TGB
Balslev et al. 2000 (2)	12; f	not known	sympt	30 mg	not known	CBZ, VGB	not done	Dosage reduction TGB	Discontinuation of TGB
Balslev et al. 2000 (3)	17; f	not known	krypt	25 mg	not known	TOP, LTG	not done	Dosage reduction TGB	Reduction of TGB
Piccinelli et al. 2000	12; m	11 yr	sympt	30 mg	not known	VPR ca.900 mg	Bifrontal sharp slow waves (3–4/s)	Dosage reduction TGB	Reduction of TGB to 15 mg
Ettinger et al. 1999 (1)	28; f	23 yr	sympt	36 mg	6–8 wks	VPR 500 mg	Blunt delta (2.5–3/s) and sharp slow waves	Discontinuation TGB	Discontinuation of TGB
Ettinger et al. 1999 (2)	28; m	25 yr	krypt	32 mg	2–3 mo	LTG 500 mg	Blunt delta (2.5–3/s) sharp slow waves	Benzodiazepine i.v.	Discontinuation of TGB
Eckardt and Steinhoff 1998 (1)	28; f	not known	krypt	30 mg	4–8 wks	GBP 1600	Generalized sharp slow waves	Benzodiazepine i.v.	Discontinuation of TGB
Eckardt and Steinhoff 1998 (2)	39; f	33 yr	sympt	40 mg	8–10 wks	CBZ 1600, VPA 2400	Generalized sharp slow waves	Discontinuation TGB	Discontinuation of TGB
Holtkamp et al. 1999	66; f	not known	not known	40 mg	7–8 wks	LTG 100 mg, CBZ 1500 mg	Generalized rhythmic delta waves	Benzodiazepine i.v.	Reduction of TGB to 15 mg
Trinka et al. 1999	21; f	15 yr	krypt	30 mg	2–3 mo	CBZ 1200 mg, VGB 1000 mg	Rhythmic generalized delta waves (2.5–3/s)	Benzodiazepine i.v.	Discontinuation of TGB
Schapel and Chadwick 1996 (1)	46; f	25 yr	not known	48 mg	not known	CBZ 400 mg, LTG 400 mg	not done	Benzodiazepine i.v.	Reduction of TGB 42 mg
Schapel and Chadwick 1996 (2)	49; m	41 yr	not known	54 mg	not known	CBZ 1200 mg, PHT 350 mg	not done	Benzodiazepine i.v.	Discontinuation of TGB
Schapel and Chadwick 1996 (3)	19; m	18 yr	sympt	60 mg	not known	LTG 400 mg, VGB 3000 mg	not done	Spontaneous	TGB continued unchanged
Walton et al. 1994	28; m	not known	sympt	not known	not known	not known	Rhythmic slow delta waves	Discontinuation TGB	not known
Case 1	29; m	8 yr	krypt	30 mg	18 mo	CBZ 600 mg	Rhythmic delta (2–3/s) and sharp waves	Benzodiazepine i.v.	Discontinuation of TGB
Case 2	30; f	7 yr	krypt	25 mg	3 wks	VPA 1650 mg, TOP 100 mg	Rhythmic delta (2–3/s) and sharp waves	Benzodiazepine i.v.	Discontinuation of TGB
Case 3	20; f	10 yr	krypt	25 mg	2 months	none	Rhythmic delta (2–3/s) and sharp waves	Discontinuation TGB	Discontinuation of TGB

could control the convulsive seizures but produced a hyporeactive behavioural state with rhythmic spike-wave patterns of high amplitude in the EEG. This state and the EEG pattern could be reproduced even in normal rats[4]. In hippocampal slices of Wistar rats, tiagabine developed a proconvulsive effect at higher concentrations[20].

On a functional level, Richards *et al.*[26] suggest that absence seizures may arise from GABA-mediated thalamic inhibition. Lancel *et al.*[32] found that tiagabine enhanced slow delta-activity during non-REM-sleep of rats, whereas GABA-A-receptor agonists did not have this effect. They assumed that GABA-B-mediated, slow postsynaptic hyperpolarization could enhance rhythmic oscillations of thalamic neurons during sleep. A recent report of tiagabine-induced frontal NCSE[11] implies that similar effects could arise from a GABA-effect on frontal and/or temporal neuronal circuits.

On the receptor level, Chan and Young[27] demonstrated that inhibition of neuronal GABA-reuptake and the following elevation of GABA-concentration in the synaptic cleft activates presynaptic GABA-B-receptors and thus shortens the GABA-A-receptor mediated inhibitory postsynaptic potential by reducing the synaptic release of GABA.

This could explain the immediate effect of benzodiazepines on tiagabine-induced NCSE. Benzodiazepines have a significant effect only on GABA-A-receptor mediated inhibition. In a situation where the synaptic GABA-level is reduced by activated GABA-B-receptors, benzodiazepines can enhance the effect of the remaining GABA without further decreasing the level by activating GABA-B-receptors. This point of view is supported by the report of a baclofen (also GABA-B-agonist)-induced NCSE[28] and some experimental data concerning the effect of baclofen on rat models of absence seizures[29].

The reason why NCSE occurs only in a relatively few patients but within the therapeutic range of the drug, remains unclear. On the basis of the reported cases, no potential risk factors could be identified. Furthermore, there is no explanation why patients with partial seizures and no anamnestic or encephalographic data for the presence of additional idiopathic generalized epilepsy suffer from this effect of tiagabine. Perhaps a hitherto unknown sensibility for absence seizures respectively NCSE generating structures to GABA-mediated inhibition is unmasked by a sudden and unmeasurable rise of tiagabine serum concentration. Moreover, an increased expression of presynaptic GABA-B-receptors is a possible reason for the unforeseen occurrence of NCSE in some predisposed patients.

In spite of the good anticonvulsant effect and relatively few side effects, the occurrence of NCSE is a rare but underestimated adverse event during tiagabine therapy. To elucidate possible risk factors and underlying pathomechanisms, cases of NCSE during tiagabine therapy should be reported. Episodes of decreased responsiveness during therapy should be monitored thoroughly by clinical examination as well as EEG.

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